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Developing a novel ambulatory total parenteral nutrition-dependent short bowel syndrome animal model

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ABSTRACT

Background: Short bowel syndrome (SBS) results from extensive bowel resection. Patients with SBS require total parenteral nutrition (TPN) for survival. Understanding mechanisms contributing to TPN-associated liver injury and gut atrophy are critical in developing SBS therapies. Existing SBS models using tethered animals have significant limitations and are unlike ambulatory human SBS patients. We hypothesized that we could induce SBS in piglets and develop an ambulatory TPN-SBS model.

Material and methods: Eighteen neonatal pigs received duodenal and jugular catheters. They were fitted with a jacket holding TPN and a miniaturized pump. Six piglets had 90% small bowel resection and catheter placement (SBS group). Non-SBS piglets were randomized into enteral nutrition (EN) or TPN.

Results: Bowel resection was successfully accomplished in SBS animals. Weight gain was similar in all groups. SBS animals had increased serum bilirubin compared to EN. Mean conjugated bilirubin ± SD was 0.045 ± 0.01 for EN, ($P = 0.03$ EN *versus* TPN and $P = 0.03$ SBS *versus* EN) and 1.09 ± 1.25 for TPN, ($P = 0.62$ TPN *versus* SBS). Gut density was reduced in the TPN group compared to EN and SBS groups. Mean gut density ± SD was 0.11 ± 0.04 for TPN ($P = 0.0004$ TPN *versus* SBS and $P = 0.00007$ TPN *versus* EN) and not statistically different for EN *versus* SBS ($P = 0.32$).

Conclusions: We created a novel, ambulatory TPN-SBS model using piglets, mimicking long-term TPN delivery in human SBS patients. Our model demonstrated TPN-related conjugated hyperbilirubinemia and compensatory gut hypertrophy, as noted in humans with SBS. This model holds great potential for future research.

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Introduction

Short bowel syndrome (SBS) is an often debilitating condition that results from bowel resection usually secondary to necrotizing enterocolitis, gastroschisis, inflammatory bowel disease, ischemic injury, or trauma.[1] Patients with SBS require total parenteral nutrition (TPN) for survival.[2,3]

TPN is known to cause liver injury as well as significant morbidity and mortality in adult and pediatric populations,[4,5] the mechanisms of which remain elusive and are the major focus of ongoing research.[6,7]

Efforts to understand mechanistic pathways contributing to TPN-associated injury as well as the development of ameliorative and preventative strategies are critical in the ongoing care for such patients.[8,9] A key component of such endeavors is the availability of model systems replicative of human SBS.

Testing systems using a tethered animal with indwelling catheters are not ideal due to short duration TPN therapy secondary to animal stress from a lack of free mobility.[10,11] Animal stress has been shown to cause alterations in hepatobiliary receptors as well as intestinal motility, ion secretion, and intestinal permeability.[12] Additional concern is the viability of long-term indwelling catheters that are prone to dislodgement in traditional fixed tethered systems. Conversely, in human SBS patients, TPN can be delivered long term in an unobstructed, ambulatory manner.[13-15]

Hypothesis

Given this predicament, we hypothesized that we could develop an ambulatory model of short bowel syndrome utilizing neonatal pigs that undergo 90% surgical bowel resection. Such animals would be maintained on TPN, infused via secured catheters using miniaturized infusion pumps carried by the animal thus permitting completely untethered animal mobility and nutrition delivery. This would be a significant step forward in establishing a robust model to test SBS and a platform for future mechanistic studies.

Methods and materials

Animal procurement

Saint Louis University (SLU) is a registered research facility with the United States Department of Agriculture. The study was initiated on approval by the Institutional Animal Care and Use Committee of SLU (SLU No. 2657, US Department of Agriculture registration 43-R-011) and conducted in accordance with the *Guide for the Care and Use of Laboratory Animals*.

Seven to 10 d old, term neonatal pigs were used for this study. Animals were procured from an approved class A vendor. Animals were identified by ear tags. On arrival they were immediately placed in heated cages.

Acclimatization and housing

In accordance with University guidelines, animals were acclimatized for 3 d on arrival. Piglets were fed *ad lib*, swine milk replacer formula (LitterLife; Merrick's Inc, Middleton, WI) with close monitoring of their daily intake. All animals were kept in a thermally controlled environment for the duration of the study at temperatures mandated by the facility's veterinarian.

Surgery and catheter placement

Following 3 d of acclimatization, the piglets underwent surgery for creation of iatrogenic short bowel syndrome and placement of both jugular and duodenal catheters. Each piglet was taken to the veterinary operating room and placed in an individual chamber containing 3% to 5% isoflurane for anesthetic induction. Subsequently, the animal was transferred to a heated surgery table. Using a cone mask, appropriate anesthesia was maintained (2%-4% isoflurane). Oxygen saturation, body temperature, heart rate, and the respiratory rate were continuously monitored throughout the surgical procedure. Once deeply anesthetized, the neck and abdomen were surgically prepared and draped for aseptic surgery.

Jugular catheter placement

Jugular catheters were placed in the right and left jugular vein by a vascular cut down technique. The catheters were secured to the vessel via a purse string suture. Patency was confirmed by injecting 3 mL heparinized saline. The catheters were subsequently tunneled subcutaneously to exit the skin just caudal to the scapulae. The catheter was then sutured to the skin via a catheter flange. To limit catheter slide, medical grade silicone glue was applied to additionally secure the catheter.

Duodenal catheterization

A midline 5-inch abdominal incision was made cranial to the umbilicus. Placement of a catheter into the duodenal lumen was performed as previously published.[10] Once the catheter was secured and tunneled, we proceed with 90% mid-small bowel resection.

Creation of short bowel

A 50 cm segment of the bowel proximal to the ileocecal valve as well as a 50 cm segment distal to the ligament of Treitz was identified. We measured the bowel using sterile silk ribbon placed along the antimesenteric border of the gently stretched small intestine. Using doyen-clamps, the proximal and distal ends were clamped to prevent gross contamination. The small bowel in between these two segments was resected using electrocautery and measured outside of the piglet (Fig. 1A).

Once the resected segment was freed from the mesentery, the doyen-clamped ends of each remnant bowel section (jejunum and ileum) were brought together. Stay sutures at the mesenteric and antimesenteric borders were used to